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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/340,283	06/25/99	MESSING R	GALO-007/01U

EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/340,283	Applicant(s) MESSING ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,29,31-33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) *1-9,11-28 and 40-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,29,31,33 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Response/amendment filed 6-25-01 has been entered.

2. Claims 30 and 34 have been cancelled.

Election/Restrictions

3. Claims 1-9 , 11-28, and 40-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

4. This application contains claims 1-9, 11-28, and 40-53 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Claims 10 and 29, 31-33 and 35-39 are instantly under consideration.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10 and 29, 31-33 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 12-18-00.

Response to Arguments

Applicant's arguments filed 6-25-01 have been fully considered but they are not persuasive. Following issues, pertaining to the enablement of the claimed invention, were raised in the previous office action:

the method of testing the PKC-epsilon modulatory activities of a compound in an in vitro system or in an in vivo system; can the results obtained in vitro be extrapolated to in vivo or can an effect on the activity of PKC-epsilon in vitro be reproduced in vivo when the same compound is given to an animal in vivo; can effects of a compound on the activity of PKC-epsilon be considered as an indicator of its anxiety modulatory activity based on the data obtained in the PKC-epsilon null mutant mouse of the claimed invention, particularly when the results obtained in the male and female mice are not in agreement and it is not clear whether there is a clear correlation between anxiety and PKC-epsilon and therefore there is no evidence that a compound that alters the activity of PKC-epsilon activity will modulate anxiety. Other issues were : what would be cosidered a subject, that could be used for determining efficacy of a compound in modulating the state of anxiety; could any animal be a subject for determining efficacy of a compound in modulating the activity of anxiety? Could an animal that had more than one characteristic be used in the method and if any of the symptoms listed above were present in an animal, could the animal still be an appropriate subject for the method; how would an artisan have determined whether a change in the listed behaviors is only because of anxiety, not because of some other reasons; it is not clear from the disclosure whether female mutant mice (null for PKC-epsilon) have reduced anxiety-related characteristics; and although the specification teaches a PKC-epsilon null mutant mouse, a wild type mouse that would not have any anxiety characteristics would be used in the method. In other words, it was not clear how results obtained in the animals be indicative of anxiety animal model in view of the marked differences in the behavior phenotype of six inbred strains of mice. Furthermore, it is not clear as to how the characteristics of the test animal recited in the claims could be used to reliably determine that a compound has anxiety

modulatory effect. There was no evidence that the changes seen in GABA receptor function as measured by chloride transport is specific to PCK-epsilon mediated changes in anxiety, because a compound that inhibits only PKC-epsilon in a purified preparation may inhibit other enzymes or other isoforms of PKC. How would inhibition of partially purified enzyme preparation or cell lysate (containing other enzymes) by a compound can be relied upon for anxiety modulatory activity of the compound? For example, if a broad kinase inhibitor, that inhibits different kinases, changed anxiety due to its nonspecific inhibitory activity, such an effect would not be specific for PKC-epsilon or even PKC.

Regarding the issue of the method of testing the PKC-epsilon modulatory activities of a compound, applicants have stated that claims 32-34 are in vitro methods. However, claim 32 does not recite an in vitro method because it only says exposing a functional PKC epsilon to a test compound which means it could be both in vitro as well as in vivo. Claim 33 recites that exposing is performed in a cell which again would read on both an in vivo and an in vitro assay. Regarding the issue of the extrapolation of the in vitro results to in vivo system, applicants have argued that the question is not applicable to the claims as written. However, this argument is not persuasive because applicants' statement that claim 32 is drawn to an in vitro test is not true because it reads on both in vitro and in vivo methods. Applicants argue that the method is drawn to measuring symptoms of anxiety not PKC epsilon acitivity, again it is reiterated that the mediator of the effect is PKC-epsilon and if there was no correlation between the compound's action on PKC-epsilon activity and anxiety, how could one know that the anxiety symptom modulation is because of the effect of compound on PKC-epsilon, not on any other PKC isomer or any other enzyme or pathway. Applicants have further stated that they did not agree with the Examiner's contention that it was not clear whether the effects of a compound on the activity of PKC-epsilon be considered as an indicator of its anxiety modulatory activity. Applicants argue that applicant has proven the link between PKC-epsilon activity and anxiety as shown by the PKC-epsilon null mice. In response it is reiterated that Applicant's results do not clearly establish the link between PKC-epsilon and anxiety since male and female mice do not show

same phenotype, rather they show different characteristics, therefore, the link between PKC-epsilon and anxiety is not well established. For example: the male and female transgenic mice disclosed in the specification have different characteristics, such as performance in the plus maze, body weight etc. As noted in the previous office action, the results obtained in the female mice were opposite of male mice and since the method does not recite use of a male or female mice, an artisan would not know whether to use a male animal or female mice in the methods. Furthermore, the issue is also of specificity of a compound's effect on PKC-epsilon activity and anxiety modulation. As noted in the previous office action, there are several observations that question whether a compound that affects anxiety would do so due to its specific effect on PKC-epsilon not any other enzyme (see last paragraph on page 6 of the previous office action).

Applicants have also filed a 1.132 declaration by the co-inventor Robert O. Messing. The inventor agrees with the Examiner's contention that male and female mice differ with respect to anxiety and PKC-epsilon and that male mice are used in maze test and that female rodents are not reliable for this test (see paragraph #2 on page 2 of the declaration. The declaration compared the anxiety level of wild type and mutant mice from two genetic backgrounds and state that loss of PKC-epsilon was associated with reduced anxiety. However, these arguments do not address the issue: whether the modulation of a behavior associated with anxiety due to treatment with a compound is because of the effect of the compound on PKC-epsilon. Inventor's results only show that PKC-epsilon null mutation causes decrease in anxiety level of the mutant mice, it does not indicate that the decrease in anxiety is due to PKC-epsilon, not any other enzyme or metabolic pathway that was dependent on PKC-epsilon, and when a wild type animal used in the claimed method, an artisan would not be able to differentiate whether the changes in anxiety was due to PKC-epsilon or other enzymes or pathways. In other words, there is no conclusive evidence in the prior art or in the specification to support applicants' contention that one can screen for a compound in a wild type animal for an anti-anxiety effects of the compound and that the effect of the compound on anxiety would be mediated by PKC-epsilon.

Regarding the issue of a subject and can any animal be a subject for determining efficacy of a compound in modulating anxiety, applicants have amended claims to recite "a test animal subject to anxiety". However, these arguments are not persuasive because, first, it is not clear what do the applicants mean by "a test animal subject to anxiety" and if the applicants meant "a test animal subject prone to develop anxiety", the specification does not describe an animal that is prone to develop anxiety. Second, the prior art at the time of the invention did not teach that PKC-epsilon was associated with anxiety. In fact, only publication is from the inventor's group published in 1999, (see reference D64 in the IDS filed 9-29-00), a year after the effective filing date of the application.

It is reiterated that the claimed method is based on the observation that null mutation of PKC-epsilon gene results in a decrease in anxiety level in a knockout transgenic mouse. However, it is not clear as to how total lack of PKC-epsilon can be correlated with the claimed method wherein a compound would only modulate PKC-epsilon activity- presumably by altering the level of PKC-epsilon or by altering the enzyme activity. It is noted that the specification does not provide any guidance as to whether complete elimination of PKC-epsilon or complete inhibition of PKC-epsilon activity, similar to the knockout mouse, is possible using a compound. Alternatively, there is no teaching or guidance in the specification as to what level of alteration in PKC-epsilon activity or level would have cause anxiety in a test animal. The specification does not provide any evidence whether change in the PKC-epsilon activity in an animal would have decreased anxiety status of the animal or whether any of the parameters used in the methods- e.g., behavior in a maze, would have altered if PKC-epsilon activity was inhibited in the test animal. Alternatively, the specification does not provide any guidance in the specification as to whether an increase in PKC-epsilon activity would have resulted in an increase in the anxiety status of the animal. In other words, the specification does not teach whether in an animal there is any correlation between the level of PKC-epsilon and anxiety level of the normal.

Next regarding the issue of the parameters, applicants state that the behaviors listed are not innate characteristics of desirable subjects and that the

claimed invention is a comparative test. Applicants have further indicated that test subject should not exhibit these behaviors in the normal state but should only exhibit them when stressors are applied, however, the claim does not recite this limitation. It is noted that as currently recited, claimed invention would encompass a wild type animal that may or may not have anxiety, however, such animals (without anxiety) can not be used in the method. As noted in the previous action, it is not clear as to how would an artisan have determined whether a change in the listed behaviors is only because of anxiety mediated by PKC-epsilon and not due to any other biochemical or physiological pathway.

Applicants did not respond to other issues such as: there is no evidence that the changes seen in GABA receptor function as measured by chloride transport is specific to PCK-epsilon mediated changes in anxiety because a compound that inhibits only PKC-epsilon in a purified preparation may inhibit other enzymes or other isoforms of PKC and how would inhibition of partially purified enzyme preparation or cell lysate (containing other enzymes) by a compound can be relied upon for anxiety modulatory activity for example, a broad kinase inhibitor may inhibit all the kinases, and such an effect would not be specific for PKC-epsilon or even PKC.

In conclusion, the specification is not enabling for the claimed method because the specification fails to provide sufficient evidence whether a compound that affects PKC-epsilon would have anxiety modulatory activity and the specification fails to provide sufficient guidance as to what would have been considered a subject or an animal model of anxiety and an artisan of skill would have required undue experimentation to make and use the claimed invention.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> a. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

9. Claim 10, 29, 31, and 35-39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 is vague and indefinite because it is unclear as to what is meant by the phrase "a test animal subject to anxiety."

Claims 35 is vague and indefinite because it is unclear as to what is meant by the phrase "an animal subject to anxiety."

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

b. Ram R. Shukla, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER